Remarks

Claims 41-52 are pending in this application. No claim amendments are made in this paper, and thus, no new matter has been introduced.

Applicant appreciates the Examiner's withdrawal of the rejections previously outstanding in this application. However, new rejections are set forth in the Office Action. Applicant respectfully submits that all of the pending claims are allowable for at least the following reasons.

A. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 3-7 of the Office Action, claims 41-52 are rejected over Scott *et al.*, *Br. J. Pharmacol.*, 111: 97-102 (1994) ("Scott"), in view of WO 94/00114 by Young *et al.* ("Young") and an excerpt from *Harrison's Principles of Internal Medicine*, 13th Ed., pp. 162-168 (1994) ("Harrison"). Applicant respectfully traverses this rejection.

In the Office Action, it is alleged that the claims are obvious based on the Examiner's assertion that: 1) Scott purportedly discloses that didesmethylsibutramine has "a similar pharmacological profile to the parent compound in vivo, but [is] up to 100 fold more potent than sibutramine ... in vitro" (Office Action, page 4); 2) Scott also discloses that "sibutramine and [didesmethylsibutramine] have no significant affinity for muscarinic receptors" (*Id.*); 3) Young discloses the use of (-) sibutramine and its doses and routes of administration (*Id.* at pages 4-5); and 4) Harrison discloses that symptoms of narcolepsy may be treated by antidepressants (*Id.* at page 6). Applicant respectfully points out that, even if all of the allegations made by the Examiner were taken true, the pending claims cannot be obvious over the combination of the references cited by the Examiner.

First, Applicant respectfully points out that none of the references cited by the Examiner discloses or suggests anything whatsoever regarding enantiomerically pure (S)-didesmethylsibutramine. In this regard, it appears that the Examiner believes that Scott's disclosure of racemic didesmethylsibutramine and Young's disclosure of (-) sibutramine would somehow point to enantiomerically pure (S)-didesmethylsibutramine. However, Applicants respectfully point out that Young's disclosure of (-)-sibutramine does not teach or suggest anything with regard to the desirability of one particular enantiomer of didesmethylsibutramine. In particular, Applicant respectfully points out that Scott's disclosure that racemic didesmethylsibutramine may have pharmacological properties similar to racemic sibutramine cannot provide basis to conclude that (S)-didesmethylsibutramine may be equated with (-)-sibutramine in the same way. Therefore,

in the absence of any suggestion in Scott or Young, or in prior art in general for that matter, Applicant respectfully submits that this rejection should be withdrawn for this reason alone.

Second, even assuming, *arguendo*, that the references somehow suggest (S)-didesmethylsibutramine, the claims are not still not obvious over the combination of references cited by the Examiner. This is because, as the Examiner recognizes, Scott and Young are completely silent regarding the treatment of narcolepsy. In this regard, the Examiner appears to suggest that Harrison's disclosure that antidepressants may be employed to relieve the symptoms of narcolepsy would somehow render obvious the use of (S)-didesmethylsibutramine in treating narcolepsy.

However, Applicant respectfully points out that the blanket statement that certain symptoms of narcolepsy can be treated with "antidepressants" does not provide any basis to conclude that any and all antidepressants are effective in treating such symptoms. As well-settled, each obviousness determination should rest on its own facts. (*See, e.g., In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) ("Generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from another.")). In other words, the statement made in Harrison referred to by the Examiner, which broadly and generally refers to "antidepressants," cannot provide any insight or suggestion with regard to the use of any specific antidepressant, much less sibutramine, further less didesmethylsibutramine, and yet further less enantiomerically pure (S)-didesmethylsibutramine.

This is further evidenced by the disclosure of Harrison itself. In the very portion referred to by the Examiner, Harrison, while indicating that antidepressants may be effective in treating certain symptoms of narcolepsy, and that protriptyline is commonly used, also indicates that "compounds including viloxzine hydrochloride and fluoxetine are under evaluation" for narcolepsy. (Harrison, page 167, last paragraph). This clearly implies that each and every antidepressant must be separately evaluated for their efficacy and/or safety for the treatment of narcolepsy, and that purported efficacy of one antidepressant may <u>not</u> be interpolated to any other antidepressants. Thus, Harrison, in combination with Scott and Young, would not have provided any meaningful guidance to a skilled practitioner at the time of conception of the presently claimed invention. For this additional reason, Applicant respectfully submits that the rejection of the claims should be withdrawn.

Finally, Applicant respectfully points out that, taking the prior art in general, those skilled in the art would not have been led to investigate didesmethylsibutramine, much less enantiomerically pure (S)-didesmethylsibutramine. In this regard, Applicant

respectfully invites the Examiner's attention to Luscombe *et al.*, *Neuropharmacology*, 28(2): 129-134 (1989) ("Luscombe"), a copy of which is attached hereto as **Exhibit A**. As the Examiner will see, Luscombe discloses that "the secondary and primary amine metabolites" of sibutramine exhibit similar *in vivo* pharmacological activity to the parent compound. (*See* Luscombe, Abstract and Table 1 on page 131). Thus, despite Scott's purported disclosure that didesmethylsibutramine may be 100 times more potent than sibutramine *in vitro*, those of ordinary skill in the art reading Luscombe's disclosure would not have been led to use didesmethylsibutramine on the face of the disclosure that no difference in pharmacological activity *in vivo* is observed for didesmethylsibutramine.[1, 2] This is particularly true for the claimed method, which involves the administration of didesmethylsibutramine to a patient.[3] Therefore, Applicant respectfully submits that the rejection of the claims should be withdrawn for this additional reason.

In the second part of the Office Action, claims 42-27 are rejected over Scott, in view of Young and Harrison, and further in view of Gundlah *et al.*, *Pharmacology and Experimental Therapeutics*, 283(2): 581-591 (1997) ("Gundlah"). In particular, it is alleged that those skilled in the art "would have been motivated to combine the teaching of" Scott, Young, Harrison, and Gundlah to "create a method of treating narcolepsy comprising administering to a patient" didesmethylsibutramine. (Office Action, page 8). Applicant respectfully disagrees.

Applicant respectfully reiterates that even when Gundlah is added to the combination, there is still no disclosure or suggestion of enantiomerically pure (S)-didesmethylsibutramine or the treatment of narcolepsy using (S)-didesmethylsibutramine, for the reasons discussed above.

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[1] And even more so for (S)-didesmethylsibutramine for this and other reasons discussed above.

[2] Further in this regard, Applicant notes that the Examiner refers to the portion of Scott that allegedly provides the suggestion to use didesmethylsibutramine. In particular, the Examiner cites to the portion that discloses "sibutramine and [didesmethylsibutramine] may result in fewer and less pronounced side-effects than the tricyclic antidepressants." (Office Action, page 6). However, Applicant respectfully points out that Scott does not disclose or suggest anything with regard to the desirability of didesmethylsibutramine when compared to sibutramine itself. Absence of such disclosure, along with Luscombe's disclosure that sibutramine and didesmethylsibutramine have similar in vivo activity, would have discouraged those skilled in the art to investigate didesmethylsibutramine, much less (S)-didesmethylsibutramine.

[3] In this regard, Scott's disclosure that didesmethylsibutramine is reportedly more potent than the parent compound *in vitro* is irrelevant to the patentability of the claimed methods since *in vivo* activity is what matters when determining whether an agent should be "administered to a patient." Therefore, those skilled in the art would not have acquired any suggestion whatsoever from Luscombe's disclosure of *in vitro* activity.

In this regard, Applicant respectfully points out that Gundlah adds nothing to the substance of the rejection. The Examiner cites to the portion of Gundlah that purportedly discloses that "[didesmethylsibutramine] produces a dose-dependent increase in hypothalamic 5-HT following systemic administration ... to rats." (Office Action, page 8). However, Applicant respectfully submits that such disclosure is nothing more than a mere confirmation of the earlier knowledge that didesmethylsibutramine behaves similarly in vivo as sibutramine, as discussed above in connection with Luscombe. Indeed, Gundlah discloses that both sibutramine and didesmethylsibutramine produce similar dose-dependent increase in hypothalamic 5-HT. (*See* Gundlah, page 6 provided by the Examiner). Therefore, Gundlah merely confirms that sibutramine and didesmethylsibutramine behave in similar ways in vivo, as disclosed by Luscombe, and thus, does not add anything additional to the combination of Scott, Young, and Harrison. Therefore, for at least the reasons discussed above in connection with Scott, Young, and Harrison, Applicant respectfully submits that the rejection of the claims should be withdrawn.

Conclusion

For at least the foregoing reasons, Applicant submits that all of the pending claims are allowable, and thus, respectfully requests that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

No fee is believed due for this submission. If any fees are required, however, please charge such fee(s) to Deposit Account No. 503013.

Respectfully submitted,

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